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EXAMINER	
SLOBODYANSKY,E	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No. 09/430,029	Applicant(s) Yano et al.
	Examiner Elizabeth Slobodyansky	Group Art Unit 1652

☒ Responsive to communication(s) filed on *Apr 9, 2001* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-48 and 55* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 3-48, and 55* is/are rejected.

☒ Claim(s) *2* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *11*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The amendment filed April 9, 2001 (Paper No. 10) amending the specification to delete references to Figures 1-14 in "Brief description of drawings", canceling claims 49-54 and amending claims 1-3, 5-11, 15, 17 and 55 has been entered.

Claims 1-48 and 55 are pending.

Rejections and/or objections not reiterated from previous Office action are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office action.

Election/Restriction

Applicant's election of Group I in Paper No. 10 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Drawings

The drawings are objected to because of the following : Figure 15 should be corrected to show that it is now Figure 1 both on the figure and in the description.

Correction is required.

Specification

Per Applicants' request, the examiner confirms that a substitute Sequence Listing and the computer readable form thereof filed April 5, 2000 have been entered.

Claim Objections

Claims 2, 3, 9 and 10 are objected to because of the following informalities:

In claim 2, the words ", said isolated DNA-fragment" appear to be redundant. Referring to "in the Sequence listing" is not necessary.

In claims 3, 9 and 10 "substitution" appears twice.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 1, 3, 6-10, 15, 17, 19 and 55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 3, 9, 10, 17 and 55 recite sequences homologous to either amino acid or nucleic acid sequences or to otherwise variants of said sequences, i.e., having at least one substitution (claims 3, 9, 10 and 55) or having one or more deletion, substitution, and/or addition (claim 17). Regarding claim 17, this amounts to any structure having the same function as a protein encoded by SEQ ID NOs: 2-7 or a gene comprising SEQ ID NO:1. This is equivalent to a claim with no structural limitations wherein an enzyme is defined by the function only. The specification discloses no identifying characteristics which would allow to recognize a structure as a member of a genus of a DNA encoding a toluene monooxygenase activity. Therefore, based on the instant disclosure, it is unpredictable either a DNA encodes a toluene monooxygenase.

With regard to claims 3, 9, 10 and 55, the structural limitations are insufficient because while a substitution is required to be conservative any amino acid residue in the sequence can be substituted resulting in a completely novel structure that is not described. Furthermore, the genus of DNAs that comprise these above DNA molecules is a large variable genus with the potentiality of encoding many different proteins. In claims 3 and 10, many functionally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus.

Thus, a DNA encoding an amino acid sequence obtained by unlimited conservative substitution of SEQ ID NO: 2 or a DNA having a nucleotide sequence of SEQ ID NO:1 with deletion, substitution, and/or addition of one or more nucleotides, lack sufficient written description needed to practice the invention of claims 3, 9, 10, 17 and 55.

Claims 6, 7 and 19 recite a DNA fragment encoding a toluene monooxygenase comprising DNA sequences encoding ORFs of a gene encoding a toluene monooxygenase. This is equivalent to claiming a gene by its coding regions only. The specification teaches one gene having the sequence of SEQ ID NO:1. The claims drawn to a gene encoding the amino acid sequence are insufficiently described in that a gene includes sequences in addition to the coding sequence such as promoters, spacers, etc. The structure of these naturally occurring sequences is empirically determined. There is no known or disclosed correlation between the function of the gene and the structure of the non-described regulatory elements and untranslated regions of the gene. Therefore, one skilled in the art would not recognize from the disclosure that applicants were in possession of the genus of genes encoding a toluene monooxygenase at the time the invention was made.

Claims 3, 7, 9, 10, 15, 17, 19 and 55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a toluene

monooxygenase encoded by sequence of SEQ ID NO:1 and a DNA encoding SEQ ID NOs:2-7, does not reasonably provide enablement for a DNA encoding a toluene monooxygenase a of an unknown amino acid sequence obtained by substitutions in SEQ ID NO:2, a DNA encoding a protein of an unknown amino acid sequence and function obtained by substitutions in SEQ ID NO:2 and a DNA obtained by one or more deletion, substitution, and/or addition in SEQ ID NO: 1 and encoding a toluene monooxygenase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7)considered in determining whether undue experimentation is required, are summarized the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant invention is directed to a gene encoding a toluene monooxygenase having the sequence of SEQ ID NO:1. It comprises several coding regions encoding proteins of SEQ ID NOs:2-7. The above claims are drawn to sequences having

structures different from SEQ ID NOS 2-7 or encoded by a modified SEQ ID NO:1 retaining the requisite function and having no claimed function.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any sequence that comprises SEQ ID NO:1 and encodes proteins of unknown structure obtained by deletion, substitution and/or addition from SEQ ID NOs:2-7 wherein said protein when aligned and linked in a certain order exhibit a toluene monooxygenase activity. This is because the specification does **not** establish: (a) regions of the protein structure which may be modified without effecting the specific requisite activity of the polypeptide of the instant invention; (B) the general tolerance of said polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Despite knowledge in the art to produce mutations in proteins, the specification fails to provide guidance as to where, and what type of (i.e., what amino acid to substitute into, add to or delete from the known sequence), changes in amino acid residues will result in a desired enzymatic activity. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in a certain activity is

extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited.

Furthermore, while recombinant and mutagenesis techniques are known, it is not routine in the art to screen large numbers of mutated proteins or genes where the expectation of obtaining similar activity is unpredictable based on the instant disclosure.

Claims 3 and 10 are drawn to a DNA encoding a protein of unknown function. The specification does not teach how to use said protein.

Therefore, one of ordinary skill in the art would require guidance, in order to make a toluene monooxygenase homologous to a toluene monooxygenase of the instant invention or a gene encoding thereof in a manner reasonably correlated with the scope of the claims. Further, one of ordinary skill in the art would require guidance, as to how to use a modified DNA as claimed in claims 3 and 10 which encodes a protein with no known function. Without such guidance, the experimentation left to those skilled in the art is undue.

Claims 1 and 15 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that *Borkholderia cepacia* KK01 or *E. coli* HB101 (pKK01)are required to practice the claimed invention. As a required element it/they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it/they is/are not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the microorganism(s). See 37 C.F.R. § 1.802.

The specification does not provide a repeatable process for obtaining the microorganism(s) and it is not apparent if the microorganism(s) is/are readily available to the public. The specification must contain the date that the microorganism(s) was/were deposited, the name of the microorganism(s) and the address of where the microorganism(s) was/were deposited.

If the deposit(s) has/have been made under the terms of the Budapest Treaty, as in case of *E. coli* HB101 (pKK01) that has been deposited under accession number FERM BP-6916 (paragraph bridging pages 48 and 49)then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his/her signature, and registration number, stating that the specific strain(s) has/have been deposited under the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 C.F.R. § 1.808.

If the deposit(s) has/have not been made under the Budapest Treaty, then in order to certify that the deposit(s) meets the criteria set forth in 37 C.F.R. § 1.801-1.809, Applicant(s) may provide assurance of compliance by an affidavit or declaration, or by a statement by an Attorney of record over his/her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

© the deposit(s) will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a viability statement in accordance with the provisions of 37 C.F.R. § 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 C.F.R. § 1.809 (d) should be added to the specification. See 37 C.F.R. § 1.803-1.809 for additional explanation of these requirements.

Claims 3, 4, 9, 10, 11, 15, 17 and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 9 and 10 are confusing. They recite "no amino acid change with code degeneration". Further, the Markush group is improper.

Claim 15 twice recites "a DNA fragment of 5.8 Kb ..." .

Claims 17 and 55 recite "the DNA fragment has a toluene monooxygenase region". A DNA fragment does not have an enzyme region. At most it can encode it. Claim 55 recites "the DNA fragment has a toluene monooxygenase region of 4.9 kb or less is functionally connected to the promoter" (emphasis added).

Claims 4 and 17 are confusing because the relationship between a vector and a DNA fragment are unclear. For the sake of expedient prosecution, the examiner will interpret the claims as drawn to a vector comprising a DNA fragment.

Claims 11 and 55 are confusing because the relationship between a vector, a promoter and a DNA fragment are unclear. For the sake of expedient prosecution, the examiner will interpret the claims as drawn to a vector comprising a promoter operably linked to a DNA fragment.

Response to Arguments

Applicant's arguments filed April 9, 2001 have been fully considered but they are not persuasive.

With regard to the insufficient written description of "gene", applicants argue that ""the non-transcription/non-translation regions in SEQ ID NO: 1 are not essential. This is clearly shown from the specification, Example 6, where tomK -tomP and tomL-tomP are cut out just before the initiation codon and linked directly to trc promoter and ribosome binding site of an expression vector to express monooxygenase activity in E. coli " (paragraph bridging pages 12 and 13). The examiner brings applicants' attention to the fact that in that case the promoter is heterologous whereas the rejection is made over a naturally occurring gene, the structure of which is unpredictable from the available data.

The examiner maintains the 112, 2nd paragraph, rejection of claims 4, 11, 17 and 55 because no explanation/support has been found on pages indicated by Applicants (paragraph bridging pages 13 and 14). Specifically, page 26, line 15, through page 27, line 1, does not recite a promoter. Page 59, lines 4-14, recites "vectors contain a trc promoter and a rrnB terminator, ..." (page 59, lines 10-12, emphasis added).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner